IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Kevy et al. Atty Dkt: 1459.008A

Serial No.: 10/765,694 Group Art Unit: 1657

Filed: January 27, 2004 Examiner: Laura Schuberg

Title: METHOD FOR THE PRODUCTION OF COAGULANT FROM ANTICOAGULATED WHOLE BLOOD

DECLARATION UNDER 37 CFR §1.132

I, Sherwin V. Kevy, citizen of the United States of America and residing at 6 Strathmore Road, Brookline, Massachusetts, USA, declare that:

1. I am a co-inventor of the claims of the above-captioned patent application.

2. I hold undergraduate and medical degrees, from the following institutions: A.B., Hobart College, Geneva, New York; and M.D., College of Physicians and Surgeons, Columbia University, New York, New York.

3. Subsequent to obtaining my medical degree, I completed internship and residency programs and served as Chief Resident in pediatrics at The Children's Hospital, Harvard Medical School, Boston, Massachusetts; additionally, I served as a teaching fellow in pediatrics, and as a clinical and research fellow in medicine (hematology) at The Children's Hospital, Harvard Medical School, Boston, Massachusetts and also as a research fellow in pediatrics at Harvard Medical School, Boston, Massachusetts.

4. I am licensed to practice medicine by the Commonwealth of Massachusetts and I am certified by the American Board of Pediatrics and have certification in Blood Banking from the American College of Pathology.

5. I have been employed by The Children's Hospital since 1961 as, sequentially, assistant physician, assistant in Hematology, Medical Director, Transfusion Service and Blood Bank and served concurrently as sequentially, an Instructor, Associate, and Assistant Clinical Professor in Pediatrics, Harvard Medical School. Currently, I am Associate Professor of Pediatrics of Harvard Medical School, Boston, Massachusetts and Medical Director Emeritus of the Transfusion Service of The Children's Hospital. I am also an investigator at CBR Institute

for Biomedical Research, Inc., Boston, Massachusetts and a consultant for Harvest Technologies Corporation, Plymouth Massachusetts.

6. I am a member of several professional organizations, including:

- American Society of Apheresis (Board of Directors 1990-present)
- American Association of Blood Banks
- International Society of Blood Transfusion
- International Society of Hematology
- Wound Healing Society
- American Society of Artificial Internal Organs

7. I served for the U.S. Public Health Service as Laboratory Chief, Clinical Center Blood Bank, Division Biologics Standards, National Institutes of Health, Bethesda, Maryland.

8. I am the author of numerous publications, textbooks, chapters and presentations relating to hematology. Examples of my work include:

- Kevy, S.V.; The storage of erythrocytes. Nathan, D.G. and Oski, F.A., ed. Hematology in Infancy and Childhood. W.B. Saunders, Philadelphia 1974.
- Sherry, S., Williams, W. Kevy, S.V and Marder, V; Hemostasis and Inhibition of Fibrinolysis: A Hematologist's Point of View. Produced by the Department of Medicine, Temple University.
- Burka, E.R., Harker, L.A., Kasper, C.K., Kevy, S.V., and Ness, P.M.; A protocol for cryoprecipitate production. Transfusion 15(4):307-311 1975.
- Kevy, S.V., Jacobson, M.S.; Comparison of Methods for Point of Care Preparation of Autologous Platelet Gel. J. Extracorporeal Technology 36(1):28-35
- Elfath, M.D., Whitley, P., Jacobson, M.S., Cranfill-Hupp, K., Kemp, D.M., McNeil, D., Sawyer, S., Bell-Dize, S., Gorlin, J.B., Kev S.V., McAteer, M.J.; Evaluation of an automated system for the collection of packed RBCs, platelets, and plasma. Transfusion 40(10):1214-1422 (2002)

9. The rejected claims are directed to a method for the production of a coagulant (for example, thrombin) from anticoagulated whole blood, the method comprising the steps of obtaining a volume of anticoagulated whole blood from a subject, mixing said anticoagulated whole blood with a precipitating agent, incubating the mixture for a time sufficient to produce a cellular and specific plasma component precipitate and a supernatant, separating the precipitate from the supernatant; and recovering the supernatant wherein said supernatant is used as a coagulant.

10. I have read the Office Action dated December 15, 2007, wherein the Examiner has rejected claims 1, 2, 7 and 19 of the present application under 35 U.S.C. §103, as obvious in view of McGinnis et al. (U.S. 2004/0120942) published June 24, 2004. The Office Action states that McGinnis discloses a method for obtaining thrombin from a whole blood preparation without having to first obtain a plasma fraction from the whole blood. According to the Office Action one of ordinary skill would have been motivated to use whole blood in the process/device of McGinnis because it would have shortened and simplified the process of obtaining thrombin. Furthermore, the Office Action maintains that one of ordinary skill would have had a reasonable expectation of success because McGinnis teaches that the device that is used for the process is suitable for use with whole blood.

11. I have read the McGinnis reference and, in my opinion, when viewed in the context of the knowledge of the skilled artisan at the time of the disclosure, McGinnis does not teach a method of obtaining thrombin directly from whole blood, that is, without first obtaining a plasma fraction nor does it suggest to one skilled in the art a reason to modify the clinically accepted method for obtaining thrombin by isolation from a plasma fraction.

12. One of skill in the art at the time of the McGinnis disclosure would have known that precipitation of an anticoagulated whole blood preparation would result in a preparation containing significant levels of cell debris and cellular proteins not present in a similarly processed plasma preparation.

13. Accordingly, until recently, the standard of practice for the production of a thrombin preparation from human blood consisted of taking a sample of anticoagulated whole blood and first removing the cells to obtain a plasma fraction. Typically, blood fractionation of this sort involves centrifuging anticoagulated whole blood to separate the blood components according to density, allowing recovery of an essentially cell-free plasma fraction. After centrifugation, the blood is separated into an upper plasma fraction, comprising ~60% of the sample volume, a lower red blood cell fraction comprising ~40%, and a thin interface layer, called the "buffy coat" that comprises the leukocytes. For preparation of thrombin from plasma, the upper plasma fraction is recovered by aspiration and further processed to obtain the thrombin preparation.

14. As late as 2005, the relevant art, including the examples in McGinnis et al., taught only the use of plasma for the production of human thrombin (See Kumar et al. *Stability of human thrombin produced from 1 ml of plasma using the thrombin processing device.* J Extra Corpor Technol. 37:390-395 2005). Preparation of thrombin from whole blood, without a plasma isolation step, was not viewed in the art as necessary or desirable.

15. A report appearing in print in the scientific literature (March 2007) establishes the desirability and feasibility of eliminating the plasma isolation step in making thrombin from whole blood, the results having been reported at the 44th International Conference of the American Society of Extra-Corporal Technology in April 2006 A copy of the article, Kumar et al., *Whole Blood Thrombin: Development of a Process for Intra-Operative Production of Human Thrombin*, J. Extra Corpor Technol. 39(1):18-23 2007, is attached hereto as Exhibit A.

16. In my opinion, therefore, one skilled in the art would not conclude, based on the disclosure of McGinnis et al., in view of the knowledge of one of skill in the art at that time, that the preparation of a thrombin preparation obtained directly from whole blood, that is, without the plasma isolation step, was either feasible or desirable. Only recently has the direct processing of anticoagulated whole blood to obtain a thrombin preparation been accepted in the art.

17. I further declare that all statements of the foregoing Declaration made of my own knowledge are true and that all statements made upon information and belief are believed true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above identified application or any patent issuing thereon.

6-13-07
Date

Sherwin V. Kevy, M.D.